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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/677,395
Filing Date: October 01, 2003
Appellant(s): LETANT ET AL.

Dominic M. Kotab
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 22 September 2008 appealing from the Office action mailed 11 April 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows: Page 5 of the Brief states "Claims in the application are: 1-24." This is incorrect. The Application contains only claims 1-18, with no claims cancelled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 00/079257 A1	**Branton et al**	**12-2000**
5,104,820	**Go et al**	**4-1992**

Stryer, Biochemistry, 2nd ed., pages 13-15 and 575 (1981).

Hoger, J. Polymer Sci., Part A: Polymer Chem., vol. 37, pages 2685-2698 (1999).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

Claims 7-8 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Branton et al (PCT International Publication Number WO 00/079257 A1, published 28 December 2000 as evidenced by Stryer (Biochemistry, 2nd ed., pages 13-15 and 575 (1981)).

Regarding claim 7, Branton et al teach an apparatus. In a single exemplary embodiment, Branton et al teach a substrate in the form of a membrane having one or more apertures formed therein (page 4, lines 22-30). Each aperture has a tapered portion with a top diameter greater than a bottom diameter and wherein in each aperture, the tapered portion transitions into a cylindrical portion having a diameter equal to said bottom diameter of said tapered portion; namely, Figure 3E shows the

claimed aperture structure. Branton et al further teach crosslinkers attached to an inner wall of said at least one aperture; namely, chemical crosslinkers are bound to the aperture (page 38, lines 24-30). Branton et al also teach chemical functional groups in the form of polymerases attached to the substrate at or near one end of the cylindrical portion of the aperture (page 38, lines 24-30). Polymerases are proteins, which comprise chemical functional groups as evidenced by Stryer. Stryer explicitly states that proteins are built form amino acids that have functional groups occurring as side chains on the residues (pages 13-15) and that DNA polymerases are protein (page 575).

Regarding claim 8, Branton et al teach apparatus of claim 7, wherein the substrate is glass (page 4, lines 19-25).

Regarding claim 16, Branton et al teach apparatus of claim 7, further comprising electrodes positioned to allow measurement of a current across the aperture; namely, conducting electrodes are provided on both sides of the membrane to enable electronic sensing (page 5, lines 20-26), and current is detected (page 8, line 30-page 9, line 5).

Regarding claim 17, Branton et al teach apparatus of claim 16, further comprising a device coupled to the electrodes for measuring the current across the aperture; namely, an ammeter or electrometer (page 7, lines 10-11).

Regarding claim 18, Branton et al teach apparatus of claim 17, wherein coupling of a chemical or biological material to the antibodies of chemical functional groups causes a change in current across the aperture, the change being detectable by the

device; namely, current is detected as a result of polymer interactions with the aperture (page 8, line 30-page 9, line 5).

In addition, it is noted that the courts have held that "while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." *In re Schreiber*, 128 F.3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997). In addition, "[A]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co. v. Bausch &Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). Therefore, the various uses recited in claim 18 (e.g., coupling a material [which is an **active step**], or causing a change in current) fail to define additional structural elements to the device of 18. Because Branton et al teach the structural elements of claim 18, the claim is anticipated by Branton et al. See MPEP § 2114.

Claim Rejections - 35 USC § 103

Claims 1-5 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branton et al (PCT International Publication Number WO 00/079257 A1, published 28 December 2000) in view of Hoger (J. Polymer Sci. Part A; Poly. Chem., vol. 37, pp.2685-2698 (1999)) as evidenced by Stryer (Biochemistry, 2nd ed., pages 13-15 and 575 (1981)).

Regarding claims 1, 3 and 12, Branton et al teach an apparatus. In a single exemplary embodiment, Branton et al teach a substrate in the form of a membrane

having one or more apertures formed therein (page 4, lines 22-30). Each aperture has a tapered portion with a top diameter greater than a bottom diameter and wherein in each aperture, the tapered portion transitions into a cylindrical portion having a diameter equal to said bottom diameter of said tapered portion; namely, Figure 3E shows the claimed aperture structure. Branton et al further teach crosslinkers attached to an inner wall of said at least one aperture; namely, chemical crosslinkers are bound to the aperture (page 38, lines 24-30).

Branton et al teach molecules in the form of polymerases attached to the substrate at or near one end of the cylindrical portion of the aperture (page 38, lines 24-30) and apertures having constraining diameters of about 2 nm (page 6, lines 20-30). Polymerases are enzymes that are proteins, which comprise chemical functional groups as evidenced by Stryer. Stryer explicitly states that proteins are built form amino acids that have functional groups occurring as side chains on the residues (pages 13-15) and that DNA polymerases are protein (page 575).

Page 7 of the instant specification also teaches aperture diameters of 2 nm as an embodiment of the instantly claimed diameters. In addition, Figures 8 and 9C of the instant specification show various macro-cycles, which comprise from six phenyl groups connected by six ethynyl groups (i.e., Figure 8) to 18 phenyl groups connected by 18 ethynyl groups (i.e., Figure 9C) as embodiments of the instantly claimed macro-cycle. Thus, a macro-cycle having a range of six phenyl groups connected by six ethynyl groups to 18 phenyl groups connected by 18 ethynyl groups would have a diameter “substantially the same” as an aperture diameter or 2 nm. Thus, the claim has

been given the broadest reasonable interpretation consistent with the teachings of the specification regarding substantially the same diameters as the tapered portion (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Branton et al do not teach an attached macro cyclic ring having a diameter substantially the same as the diameter of the cylindrical portion (i.e., claim 1) and having a rigid phenylethynyl backbone (i.e., claim 3) and functional groups attached thereto (i.e., claim 12). Thus, Branton et al teach a base apparatus that differs from the instantly claimed apparatus because Branton et al do not teach a macro cyclic ring having a rigid phenylethynyl backbone and functional groups attached thereto.

However, Hoger teaches macro-cyclic rings (i.e., claim 1) comprising rigid phenylethynyl backbones (i.e., claim 3; Abstract) attached to solid supports (Scheme 4). Hoger also teaches cyclic compound 11 of Scheme 5, which comprises six phenyl groups connected by 12 ethynyl groups and has functional groups in the form of cyano (i.e., CN) groups attached. Hoger also teaches the macro-cycles have the added benefit that they are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines). Thus, Hoger teaches the known technique of using macro-cyclic rings (i.e., claim 1) comprising rigid phenylethynyl backbones (i.e., claim 3) having functional groups attached (i.e., claim 12) immobilized on solid surfaces.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the apparatus as taught by Branton et al with the macro-cyclic ring as taught by Hoger et al with a reasonable expectation of success. The modification would result in the immobilization of a macro-cyclic ring (i.e., claim 1) comprising a rigid phenylethynyl backbone (i.e., claim 3) having functional groups attached (i.e., claim 12at the aperture. The diameter of the macro-cycle would be substantially the same as the diameter of the cylindrical portion of the aperture because the diameter of the ring of Hoger is substantially the same as the diameter of the ring exemplified by the molecules of Figure 8 and 9C of the instant specification, as well as substantially the same as the diameter of the cylindrical portion of the aperture because the apertures of Branton et al are the same (i.e., about 2 nm) as the aperture diameters on page 7 of the instant specification. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having host molecules therein that recognize guest molecules by precise complementarity as explicitly taught by Hoger et al (page 2687, column 2, lines 19-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the macro-cycles of Hoger could have been applied to the apparatus of Branton et al with predictable results because the macro-cycles of Hoger are predictably attached to and used on solid surfaces. Furthermore, the teachings of Hoger that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) clearly suggests to the

ordinary artisan that the macro-cycles of Hoger could be used to detect binding of other molecules in place of the molecules (i.e., polymerases) in the apertures of Branton et al.

Regarding claim 2, the apparatus of claim 1 is discussed above. Branton et al teach the substrate is glass (page 4, lines 19-25).

Regarding claim 4, the apparatus of claim 1 is discussed above. Hoger et al also teach the attachment of biological or chemical probes to the macro-cyclic ring; namely, guest molecules are bound to said macro-cyclic rings, which as the added advantage of allowing binding of additional guest members so that chemical reactions can be induced between the guests (page 2687, last 10 lines) and that the macro-cycles can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines).

Thus, Hoger teaches the known technique of using the attachment (i.e., binding) of biological or chemical probes to the macro-cyclic ring.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus as taught by Branton et al in view of Hoger with the attachment of biological or chemical probes to the macro-cyclic ring of Hoger with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in as apparatus having the added advantage of binding of additional guest members so that chemical reactions can be induced between the guests as explicitly taught by Hoger (page 2687, last 10 lines). In addition, it would have been obvious to the ordinary artisan that the known technique of using the attachment of biological or chemical probes to the macro-cyclic ring as taught by Hoger

could have been applied to the apparatus of Branton et al in view of Hoger with predictable results because the technique predictably result in macro-cycles attached to probe molecules. Furthermore, the teachings of Hoger that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) clearly suggests to the ordinary artisan that the macro-cycles of Hoger could be used to detect binding of other molecules in place of the molecules (i.e., polymerases) in the apertures of Branton et al.

Regarding claim 5, the apparatus of claim 4 is discussed above. Branton et al further teach the biological probe comprises a single strand sequence of DNA; namely, nucleic acids are bound to the molecules (i.e., polymerase catalysts) attached to the aperture (page 30, lines 5-15). Therefore, the modification of the apparatus of Branton et al with the teachings of

Regarding claim 13, the apparatus of claim 1 is discussed above. Branton et al teach electrodes positioned to allow measurement of a current across the aperture; namely, conducting electrodes are provided on both sides of the membrane to enable electronic sensing (page 5, lines 20-26), and current is detected (page 8, line 30-page 9, line 5).

Regarding claim 14, the apparatus of claim 13 is discussed above. Branton et al also teach a device coupled to the electrodes for measuring the current across the aperture; namely, an ammeter or electrometer (page 7, lines 10-11).

Regarding claim 15, the apparatus of claim 14 is discussed above. Branton et al further teach coupling of a chemical or biological material to the antibodies of chemical functional groups causes a change in current across the aperture, the change being detectable by the device; namely, current is detected as a result of polymer interactions with the aperture (page 8, line 30-page 9, line 5).

In addition, as noted above, apparatus claims cover what a device *is*, not what a device *does*. Therefore, the various uses recited in claim 15 (e.g., coupling a material [which is an **active step**], or causing a change in current) fail to define additional structural elements to the device of 15. Because the prior art teaches the structural elements of claim 15, the claim is obvious over the prior art.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Branton et al (PCT International Publication Number WO 00/079257 A1, published 28 December 2000) in view of Hoger (J. Polymer Sci. Part A; Poly. Chem., vol. 37, pp.2685-2698 (1999)) as evidenced by Stryer (Biochemistry, 2nd ed., pages 13-15 and 575 (1981)) as applied to claim 1 above, and further in view of Go et al (U.S. Patent No 5,04,820, issued 14 April 1992).

Regarding claim 6, the apparatus of claim 1 is discussed above.

Branton et al also teach Figure 5A, which shows a substrate comprising dielectric layer 50, silicon wafer 130, a layer of silicon nitride 134, conductive layer 46 (pages 19 and 24), and an additional layer of silicon oxide (i.e., silicon dioxide; page 19, lines 19-25). The dielectric layer is also silicon nitride (page 25). Thus, Branton et al in view of

Hoger teach an apparatus that differs from the instantly claimed apparatus in that Branton et al and Hoger do not teach the conductive layer is silicon.

However, Go et al teach silicon has the added advantage of having a relatively high electrical conductivity and heat dissipation (column 3, lines 40-60). Thus, Go et al teach the known technique of using silicon as a conductor.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising a multilayered substrate as taught by Branton et al in view of Hoger with the silicon conductor of Go et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of having a conductor layer having relatively high electrical conductivity and heat dissipation as explicitly taught by Go et al (column 3,lines 40-60). In addition, it would have been obvious to the ordinary artisan that the known technique of using the silicon conductor of Go et al could have been applied to the apparatus of Branton et al in view of Hoger with predictable results because the silicon predictably results in a conductive element.

Claims 7 and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Branton et al (PCT International Publication Number WO 00/079257 A1, published 28 December 2000) in view of Go et al (U.S. Patent No 5,04,820, issued 14 April 1992) as evidenced by Stryer (Biochemistry, 2nd ed., pages 13-15 and 575 (1981)).

It is noted that this rejection applies to claim 7 to the extent that it is drawn to the embodiment of dependent claim 7.

Regarding claim 9, Branton et al teach the apparatus of claim 7. In a single exemplary embodiment, Branton et al teach a substrate in the form of a membrane having one or more apertures formed therein (page 4, lines 22-30). Each aperture has a tapered portion with a top diameter greater than a bottom diameter and wherein in each aperture, the tapered portion transitions into a cylindrical portion having a diameter equal to said bottom diameter of said tapered portion; namely, Figure 3E shows the claimed aperture structure. Branton et al further teach crosslinkers attached to an inner wall of said at least one aperture; namely, chemical crosslinkers are bound to the aperture (page 38, lines 24-30). Branton et al also teach chemical functional groups in the form of polymerases attached to the substrate at or near one end of the cylindrical portion of the aperture (page 38, lines 24-30). Polymerases are proteins, which comprise chemical functional groups as evidenced by Stryer. Stryer explicitly states that proteins are built form amino acids that have functional groups occurring as side chains on the residues (pages 13-15) and that DNA polymerases are protein (page 575).

Branton et al also teach Figure 5A, which shows a substrate comprising dielectric layer 50, silicon wafer 130, a layer of silicon nitride 134, conductive layer 46 (pages 19 and 24), and an additional layer of silicon oxide (i.e., silicon dioxide; page 19, lines 19-25). The dielectric layer is also silicon nitride (page 25). Thus, Branton et al teach an

apparatus that differs from the instantly claimed apparatus in that Branton et al do not teach the conductive layer is silicon.

However, Go et al teach silicon has the added advantage of having a relatively high electrical conductivity and heat dissipation (column 3, lines 40-60). Thus, Go et al teach the known technique of using silicon as a conductor.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising a multilayered substrate as taught by Branton et al with the silicon conductor of Go et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an apparatus having the added advantage of having a conductor layer having relatively high electrical conductivity and heat dissipation as explicitly taught by Go et al (column 3,lines 40-60). In addition, it would have been obvious to the ordinary artisan that the known technique of using the silicon conductor of Go et al could have been applied to the apparatus of Branton et al with predictable results because the silicon predictably results in a conductive element.

(10) Response to Argument

On page 8 of the Appeal Brief filed 22 September 2008 (hereafter the "Brief"), Appellant states that four issues are considered in the Brief. The examiner's response to Appellant's arguments is based on the order of Issues #1- #4 as presented by Appellant in the Brief, and are annotated as such therein.

Issue #1. The rejections of claims 7-8 and 16-18.

Appellant argues on pages 9-10 of the Brief that the rejection of claim 7 is improper because Branton et al does not overtly disclose any functional groups, and the examiner has relied upon Stryer for the teaching that polymerases comprise chemical functional groups.

However, as stated in the Advisory Action mailed 24 June 2008 (hereafter the "Advisory Action") and in Section 4 of the Final Office Action mailed 11 April 2008 (hereafter the "Final Action"), Branton et al specifically teaches the crosslinking of the polymerase to the aperture forms a protein solid-state complex (pages 38, lines 24-30). Thus, a thorough review of Branton et al clearly indicates that DNA polymerase is a protein. In addition, Branton et al specifically teach the Klenow fragment of DNA polymerase I (page 35, line 30-page 37, line 5). Page 17 of Stryer teaches that polypeptides are formed from amino acids, which, as stated in the Final Action, have side chains comprising chemical functional groups (See R1, R2, and R3 of Figure 2-19 on page 17 of Stryer). Pages 14-15 of Stryer clearly illustrate the functional groups present on the 20 amino acids that make up polypeptides in living systems. For example, the amino acids serine and threonine have an OH functional group (Figure 2-10, page 14). Lysine has an amine group (NH3+; Figure 2-12, page 15), and cysteine has a thiol group (i.e., SH, Figure 2-13, page 15). It is noted that paragraph 00046 of the instant specification states that amine and thiol are examples of functional groups. Page 576 of Stryer further states that DNA polymerase I is a polypeptide (i.e., protein).

It is noted that Thus, the DNA polymerase of Branton et al is a polypeptide that comprises functional groups in the side chains of the amino acids.

In addition, a review of the specification yields no limiting definition of "chemical functional groups." Thus, the side chains of the amino acids of the DNA polymerase of Branton et al comprise chemical functional groups, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "chemical functional groups" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Thus, contrary to Appellant's assertions on page 9 of the Brief, the single prior art reference of Branton et al does teach each and every element of the claim, either expressly or inherently, as required by *Verdegall Bros. v. Union Oil CO. of California.*. The identical invention is shown, in accordance with *Richardson v. Suzuki Motor Co.*, and the elements are arranged as broadly required by the claim as mandated by *In re Bond*.

Appellant argues on page 10 of the Brief that the examiner is stating that Branton et al inherently discloses functional group by disclosing a polymerase, and that the examiner's logic in asserting that DNA polymerase comprises functional groups "requires a long chain of possibilities to support the inference that Branton's polymerases have functional groups" and that "the best the Examiner can assert is that the polymerase *may* be a protein, which *may* be *based on* an amino acid with a functional group."

The examiner is indeed asserting that DNA polymerase I inherently comprises functional groups. However, contrary to Appellant's assertions on page 10 of the Brief, the examiner's logic is based on scientific fact and not on "possibilities." As detailed above, Branton et al teach DNA polymerase I. Stryer definitively states on page 576 that DNA polymerase I is a polypeptide, and further definitively states on page 17 that amino acids form polypeptide chains and that amino acids have side chains. Thus, DNA polymerase I is unequivocally a polypeptide made of amino acids having side chains comprising chemical functional groups. Thus, the inherent presence of functional groups on the DNA polymerase I is clearly based on the facts presented in Stryer, in accordance with *In re Rijckaert, In re Oelrich, In re Roberston, and Ex parte Levy* (cited by Appellant on page 10 of the Brief).

Appellant further argues on page 11 of the Remarks that proteins are reaction products of amino acids, and thus do not necessarily retain their functional groups.

However, as noted above, the chemical functional groups are in the side chains of the amino acids, which are not affected by the formation of the peptide bonds (see Figure 2-17 on page 17 of Stryer). Thus, the functional groups are still present in the DNA polymerase I polypeptide.

In addition, the formation of a peptide bond, as illustrated in Figure 2-17 of Stryer, couples a carboxylic acid of one amino acid (the CO_2- in the top left amino acid of Figure 2-17) and the amino group of another amino acid (the H3N+ group in the top right amino acid of Figure 2-17) to form the indicated peptide bind, which is an amide bond. An amide is also a chemical functional group. Thus, even if the rejection did not

rely upon the chemical functional groups in the side chains of the amino acids, the peptide bonds (i.e., amides) joining each of the amino acids in DNA polymerase I are also chemical functional groups because the specification yields no limiting definition of "chemical functional groups," and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "chemical functional groups."

Appellant again argues on page 11 of the Brief that the examiner's logic in asserting the inherent presence of chemical functional groups in DNA polymerase is established on probabilities and possibilities, and not on extrinsic evidence.

However, as detailed above, Branton et al teach DNA polymerase I. Stryer definitively states on page 576 that DNA polymerase I is a polypeptide, and further definitively states on page 17 that amino acids form polypeptide chains and that amino acids have side chains. Thus, DNA polymerase I is unequivocally a polypeptide made of amino acids having side chains comprising chemical functional groups. Thus, the inherent presence of functional groups on the DNA polymerase I is clearly based on extrinsic evidence (i.e., the facts presented in Stryer) in accordance with *In re Robinson* (cited by Appellant on page 11 of the Brief).

Thus, contrary to Appellant's assertion on page 11 of the Brief, the rejection of claim 7 is proper and is maintained.

Appellant argues on page 12 of the Brief that claims 8 and 16-18 are allowable because they depend on claim 7. Appellant presents no further arguments regarding the rejection of claims 8 and 16-18.

However, because claim 7 is not allowable for the reasons presented above, claims 8 and 16-18 are not allowable and remain rejected for the reasons of record.

Issue #2, Claims 1-5 and 12-15.

Appellant argues on pages 12-13 of the Brief that the examiner has failed to meet the *Graham* test because there is no motivation to combine the references.

However, as detailed in the rejections above, Branton et al teach a base apparatus that differs from the instantly claimed apparatus because Branton et al do not teach a macro cyclic ring having a rigid phenylethynyl backbone and functional groups attached thereto.

However, Hoger teaches macro-cyclic rings (i.e., claim 1) comprising rigid phenylethynyl backbones (i.e., claim 3; Abstract) attached to solid supports (Scheme 4). Hoger also teaches cyclic compound 11 of Scheme 5, which comprises six phenyl groups connected by 12 ethynyl groups and has functional groups in the form of cyano (i.e., CN) groups attached. Hoger also teaches the macro-cycles have the added benefit that they are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines). Thus, Hoger teaches the known technique of using macro-cyclic rings (i.e., claim 1) comprising rigid phenylethynyl backbones (i.e., claim 3) having functional groups attached (i.e., claim 12) immobilized on solid surfaces.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the apparatus as taught by Branton et al with the macro-cyclic ring as taught by Hoger et al to arrive at the instantly claimed apparatus with a reasonable expectation of success. The modification would result in the immobilization of a macro-cyclic ring (i.e., claim 1) comprising a rigid phenylethynyl backbone (i.e., claim 3) having functional groups attached (i.e., claim 12at the aperture. The diameter of the macro-cycle would be substantially the same as the diameter of the cylindrical portion of the aperture because the diameter of the ring of Hoger is substantially the same as the diameter of the ring exemplified by the molecules of Figure 8 and 9C of the instant specification, as well as substantially the same as the diameter of the cylindrical portion of the aperture because the apertures of Branton et al are the same (i.e., about 2 nm) as the aperture diameters on page 7 of the instant specification. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having host molecules therein that recognize guest molecules by precise complementarity as explicitly taught by Hoger et al (page 2687, column 2, lines 19-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the macro-cycles of Hoger could have been applied to the apparatus of Branton et al with predictable results because the macro-cycles of Hoger are predictably attached to and used on solid surfaces.

Furthermore, the teachings of Hoger that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines

19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) clearly suggests to the ordinary artisan that the macro-cycles of Hoger could be used to detect binding of other molecules; i.e., in place of the molecules (i.e., polymerases) in the apertures of Branton et al.

Thus, that in response to Appellant's citation of *Graham v. John Deere* and, the prior art of Hoger clearly provides a motivation to use the macrocyclic rings, a reasonable expectation of success, and the combination of the cited prior art results in all of the claimed limitations.

In addition, it is also noted that in response to Appellant's citation of *In re Vaeck* on page 12 of the Brief, the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith* (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007).

Further, the rejection has clearly provided a convincing line of reasoning, based on the teaching of Hoger that the macro-cycles could be used to detect binding of other molecules, as to why to ordinary artisan would have found the claimed invention to be obvious, as required by *Ex parte Clapp*.

Appellant further argues on page 13 of the Brief that neither reference teaches or suggests a macro-cyclic ring coupled to a solid substrate, as is claimed. Appellant is therefore attacking the references individually.

However, the claims are rejected under 35 USC 103(a) as obvious over the prior art. The claims are not anticipated by a single piece prior art under 35 USC 102. Thus,

it is the combination of the cited prior art that teaches all of the claim limitation, including a macro-cyclic ring coupled to a solid substrate.

Specifically, as detailed in the rejections above, Figure 3E o Branton et al shows the claimed aperture structure. Branton et al further teach crosslinkers attached to an inner wall of said at least one aperture; namely, chemical crosslinkers are bound to the aperture (page 38, lines 24-30). Branton et al also teach molecules in the form of polymerases attached to the substrate at or near one end of the cylindrical portion of the aperture (page 38, lines 24-30) and apertures having constraining diameters of about 2 nm (page 6, lines 20-30).

Hoger teaches macro-cyclic rings comprising rigid phenylethynyl backbones (Abstract) attached to solid supports (Scheme 4). Hoger also teaches cyclic compound 11 of Scheme 5, which comprises six phenyl groups connected by 12 ethynyl groups and has functional groups in the form of cyano (i.e., CN) groups attached. Hoger also teaches the macro-cycles have the added benefit that they are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines). Thus, Hoger teaches the known technique of using macro-cyclic rings comprising rigid phenylethynyl backbones having functional groups attached immobilized on solid surfaces.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the apparatus as taught by Branton et al with the macro-cyclic ring as taught by Hoger et al to arrive at the instantly claimed

apparatus with a reasonable expectation of success. The modification would result in the immobilization of a macro-cyclic ring (i.e., claim 1) comprising a rigid phenylethynyl backbone (i.e., claim 3) having functional groups attached (i.e., claim 12at the aperture. The diameter of the macro-cycle would be substantially the same as the diameter of the cylindrical portion of the aperture because the diameter of the ring of Hoger is substantially the same as the diameter of the ring exemplified by the molecules of Figure 8 and 9C of the instant specification, as well as substantially the same as the diameter of the cylindrical portion of the aperture because the apertures of Branton et al are the same (i.e., about 2 nm) as the aperture diameters on page 7 of the instant specification. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having host molecules therein that recognize guest molecules by precise complementarity as explicitly taught by Hoger et al (page 2687, column 2, lines 19-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the macro-cycles of Hoger could have been applied to the apparatus of Branton et al with predictable results because the macro-cycles of Hoger are predictably attached to and used on solid surfaces.

Furthermore, as also noted above, the teachings of Hoger that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) clearly suggests to the ordinary artisan that the macro-

cycles of Hoger could be used to detect binding of other molecules; i.e., in place of the molecules (i.e., polymerases) in the apertures of Branton et al.

In addition, it is also reiterated that under the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness.

Further, in response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant further argues on page 13 of the Brief that one cannot simply combine random chemical structures and expect to have predictable results, absent some teaching from one who has made and studied the combination.

However, as noted above, Hoger specifically teaches, that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) which clearly suggests to the ordinary artisan that the macro-cycles of Hoger could be used to detect binding of other molecules; i.e., in place of the molecules (i.e., polymerases) in the apertures of Branton et al.

In response to Appellant's argument on page 13 of the Brief that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be

recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellant argues on pages 13-14 of the Brief that the combination of Branton et al with Hoger is unpredictable with respect to crosslinker coupling between the molecule of Hoger, the diameter or the cyclic molecule, allowing the passage of a DNA molecule, and the alleged reliance of Branton et al on a "biological motor."

However, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., crosslinking of the macrocyclic ring) are not recited in the rejected claim(s) because while the claim requires crosslinkers and attachment of a macrocyclic ring, the claim does not require the attachment of the macrocyclic ring to the aperture using the crosslinkers. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, Hoger also teaches the macro-cyclic rings are attached to solid supports (Scheme 4). Thus, Hoger provides a reasonable expectation of success for crosslinking (i.e., immobilizing) the macro-cycles to a solid support (i.e., the aperture of Branton et al). In addition, as noted in the Advisory Action, Hoger clearly suggests the

construction of rigid macrocycles whose diameters do not change (page 2686, column 1, last paragraph). Also, as stated in the previous rejections, Hoger also clearly teaches that macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines). It is noted that Branton et al specifically teach the use of electrodes to induce a polymer to traverse from one side of the membrane (i.e., containing the aperture) to the other side of the membrane (page 25-, line 30-page 26, line 10). Thus, the teaching of a polymerase as a molecular motor merely represents a single embodiment of the apparatus of Branton et al.

In addition, as also noted in the Advisory Action, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record" (In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)). Thus, Appellant's arguments that the various parameters listed above are not predictable cannot take the place of evidence in the record.

Appellant argues on page 14 of the Brief that the lack of a description of cyclicals in Branton et al is evidence that such substitution was not predictable in the art.

However, the evidence that the substitution is predictable is provided by Hoger, not Branton et al, because Hoger specifically teaches that the macro-cycles are host molecules that recognize guest molecules by precise complementarity (page 2687, column 2, lines 19-25) and can act as artificial enzymes (page 2687, last two lines-page 2688, first two lines) which clearly suggests to the ordinary artisan that the macro-cycles

of Hoger could be used to detect binding of other molecules; i.e., in the aperture device of Branton et al.

Appellant argues on page 14 of the Brief that page 2689 of Hoger states that precursors coupled to the solid substrate couple together, voiding the reaction that creates the ring, thus teaching away from immobilization of the rings to a solid support.

However, page 2689 merely states that "reactions between them can take place;" i.e., that the macrocycle precursors to the ring can react with other precursors in addition to reacting with themselves to form a ring. Thus, Hoger clearly teaches that the self-condensation reactions resulting in the formation of the ring on a substrate do occur, albeit with the formation of cross-condensation side products. Therefore, while side products to occurs, there is a reasonable expectation of success, as explicitly taught by Hoger.

Further, Hoger also teaches the use of covalantly bound templates (i.e., for formation of the macro-cycles; Abstract).

Appellant argues on page 14 of the Brief the examiner has provided no showing of how such a ring could be coupled to the aperture of Branton et al.

However, Branton et al explicitly teach crosslinkers attached to an inner wall of said at least one aperture; namely, chemical crosslinkers are bound to the aperture (page 38, lines 24-30), and Hoger teaches the macro-cyclic rings are attached to solid supports (Scheme 4). Thus, the coupling of the rings of Hoger with the aperture on Branton et al at worst merely involves routine experimentation by the ordinary artisan.

Therefore, contrary to Appellant's assertions on page 14 of the Brief, the teachings of both Branton et al and Hoger provide a reasonable expectation of success and predictability for substituting the ring of Hoger for the polymerase of Branton et al.

Appellant argues on page 15 of the Brief that the proposed modification of Branton et al renders the apparatus of Branton et al unsatisfactory for its intended purpose.

However, Branton et al explicitly teaches the apparatus is used to detect a polymer molecule, "whereby the polymer molecule interacts linearly with the aperture (page 8, lines 25-30)," and the linear interaction arises from "the entirety of the channel," and may comprise a molecule (i.e., a biomolecule) that "is adjacent to, above, below, or within the membrane aperture (page 5, lines 10-25). Thus, the functionality of the apparatus of Branton et al is defined by the channel, not the molecule within. Thus, the device of Branton et al is still operable even if a molecule other than a polymerase is present.

Appellant argues on page 15 of the Brief that if Hoger's cyclical molecule were added, the DNA strand might couple with the cyclical and stop, thus no longer allowing the pulling of a DNA strand though the hole.

However, Appellant's argument that the DNA strand "might" couple with the cyclical and stop is clearly a hypothetical argument and is not supported by any evidence.

Further, as explicitly stated in the Advisory Action as reiterated above, Branton et al specifically teach the use of electrodes to induce a polymer to traverse from one side

of the membrane (i.e., containing the aperture) to the other side of the membrane (page 25-, line 30-page 26, line 10). Thus, Branton et al teach an independent mechanism, in the form of the electrodes, to gurantee the traversal of the polymer across the aperture.

Thus, the modification does not render Branton et al unsatisfactory for its intended purpose, in accordance with *In re Gordon* (cited on page 15 of the Brief by Appellant).

Appellant also argues on pages 15-16 of the Brief that Appellant's device requires the binding of an analtye to the macrocycle, in opposition to the traversal of the polymer across the aperture taught by Branton.

However, Appellant is arguing an intended use of the claimed apparatus. The courts have held that "while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." *In re Schreiber*, 128 F.3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997). In addition, "[A]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co. v. Bausch &Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). Therefore, the various uses recited in Appellant's arguments and withdrawn claim 11 (e.g., binding to the ring) fail to define additional structural elements of the claimed apparatus. Because the prior art teaches the structural elements of the claim, the claim is obvious over the prior art. See MPEP § 2114.

In addition, because Branton et al teach an embodiment wherein electrodes are used to pull the polymer through the aperture, even if a polymer were to bind to the

macro-cycle of Hoger immobilized in the aperture of Branton et al, the electrodes are clearly capable of promoting traversal of the aperture after detection of the macro-cycle-polymer complex argued by Appellant.

Appellant argues on page 16 of the Brief that the immobilization scheme listed in Scheme 4 is "not preferred" and requires "extreme approaches."

However, it is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Hoger et al that Scheme 4 results in "imperfectly isolated" compounds clearly encompasses the embodiment even thought the embodiment may not be ideal. See MPEP § 2123 [R-5].

Appellant argues on page 16 of the Brief that the Examiner appears to support the argument that Hoger teaches away from immobilized rings.

However, as noted above, while Hoger states that the immobilization scheme listed in Scheme 4 is "not preferred" and requires "extreme approaches," the teaching of Hoger et al that Scheme 4 results in "imperfectly isolated" compounds clearly encompasses the embodiment even though the embodiment may not be ideal.

Further, the teachings of Hoger do not state that immobilization is not possible or not desirable, only that immobilization is "imperfect."

Thus, contrary to Appellant's assertions on pages 16-17 of the Brief, Hoger does not teach away form immobilized macrocycles because the teaching of Hoger et al that Scheme 4 results in "imperfectly isolated" compounds clearly encompasses the embodiment even though the embodiment may not be ideal, and thus does not violate *In re Geisler* (cited by Appellant on page 16 of the Brief).

Thus, contrary to Appellant's assertions on page 17 of the Brief, claim 1 is not allowable for the reasons stated above.

Appellant argues on page 17 of the Brief that claims 2-5 and 12-15 are allowable because claim 1 is allegedly nonobvious. Appellant presents no further arguments regarding the rejection of claims 2-5 and 12-15.

However, because claim 1 is not allowable for the reasons presented above, claims 2-5 and 12-15 are not allowable and remain rejected for the reasons of record.

Issue #3. Claim 6.

Appellant argues on pages 17-18 of the Brief that claim 6 is allowable because the rejection of claim 1 is deficient for the reasons set forth in the preceding pages of the Brief. Appellant presents no further arguments regarding the rejection of claim 6.

However, because claim 1 is not allowable for the reasons presented above, claim 6 is not allowable and remains rejected for the reasons of record.

Issue #4. Claims 7 and 9.

Appellant argues on page 18 of the Brief that claims 7 and 9 are allowable because the rejection of claim 7 is erroneous. Appellant presents no further arguments regarding the rejection of claims 7 and 9.

However, because claim 7 is not allowable for the reasons presented above, claims 8 and 7 are not allowable and remain rejected for the reasons of record.

Thus, in view of the examiner's arguments above and contrary to Appellant's assertions on page 18 of the Brief, none of the independent claims are allowable, nor are any of the dependent claims.

Response to the Reply Brief of 19 February 2009.

The Reply Brief filed 19 February 2009 (hereafter the "Reply Brief") has been entered and considered but is not found persuasive for the reason(s) listed below.

A. Appellant's arguments on pages 2-3 of the Reply Brief merely reiterate arguments presented in the Appeal Brief filed 22 September 2008 (hereafter the "Brief"). These arguments are considered in full above.

B. Appellant argues on page 4 of the Reply Brief that the examiner has provided no evidence that the amide bonds (i.e., peptide bonds of DNA polymerase I) are functional groups.

However, as noted above, a review of the specification yields no limiting definition of "chemical functional groups." It is noted that page 15 of Stryer states that each of the amino acids glutamate and aspartate "contains a terminal amide group (emphasis added by the examiner)" as depicted in Figure 2-14 as the group -CONH2 in the amide side chains. Stryer also teaches on pages 13-14 that the "[t]wenty kinds of side chains" found in the amino acids control the "remarkable range of functions mediated by proteins results from the diversity and versatility of these twenty kinds of building blocks (emphasis added by the examiner)." Thus, Stryer clearly indicates that the side chain groups are functional groups, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "functional group" (In re Hyatt, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

C. Appellant's arguments on pages 4-9 of the Reply Brief merely reiterate arguments presented in the Brief. These arguments are considered in full above.

D. Appellant argues on pages 9-13 of the Reply Brief that the ruling for KSR Int'l Co. v. Teleflex, Inc (No 04-1350 (US 30 April 2007) does not apply to the instant

claims because of the alleged unpredictability of the art, that Hoger teaches away from the claimed invention, that Hoger renders Branton inoperable, that there is no reasonable expectation of success, and that the immobilization taught by Hoger does not refer to preformed rings.

These arguments were previously presented in the Brief, are considered in full above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Robert T. Crow/

Examiner, Art Unit 1634

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